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REVIEW ARTICLE

Mucoadhesive Nasal Drug Delivery System

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ABSTRACT

Nasal drug delivery system has shown great attraction in the past years to optimized therapeutic effect of drug, due to high permeability of nasal epithelial membrane so that rapid absorption of drug is possible, as compared to other non-invasive routes Nasal drug delivery system provides easy application of drug, with the possibility of self administration by removing the chance of unwanted painful condition associated with injection form of drug delivery .in this review ,the importance of nasal drug delivery system along with its advantages over other routes of administration is enlisted.

Keywords: microspheres, mucociliary clearance ,mucoadhesion.

INTRODUCTION

INTRODUCTION:

Oral drug delivery is the most desirable route for drug administration whenever systemic effects are intended. Therefore, it is not surprising that the prediction of human oral bioavailability of new drug candidates is currently targeted from the earliest stages of drug discovery and development programmes [1, 2]. However, although the oral route remains the most popular for systemic drug administrationbut low oral bioavailability of some compounds has prompted the search of more effective routes for their systemic delivery [3].

Nasal drug delivery system has shown great attraction in the past years to optimized therapeutic effect of drug, due to high permeability of nasal epithelial membrane so that rapid absorption of drug is possible, as compared to other non-invasive routes[1,2] Nasal drug delivery system provides easy application of drug, with the possibility of self administration by removing the chance of unwanted painful condition associated with injection form of drug delivery. Furthermore, lipophilic and low molecular weight drugs can easily penetrate through nasal mucosa with less degradation. Fast absorption can be achieved due to largeabsorption surface area and high vascularisation. Nasal route can be used as an alternative to parenteral incase of emergency therapy.[3,4] Nasal drug delivery system is a potential route for direct delivery of drug tothe central nervous system through olfactory region bypassing hepatic first pass metabolism.[5,6] Side byside nasal drug delivery system has some limitations like large dose cannot be administered by this routeconveniently due to administrative problems. Administration of solid formulation is quite difficult by nasalroute.[5] Fast clearance of the administered formulation

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occurs from the nasal cavity as the result ofmucociliary clearance causes poor absorption of drug.[7]These difficulties of nasal route can be minimized by utilization of various kinds of mucoadhesive polymersin the formulation. These polymers can effectively increase the retention time with improved permeationenhancing effect. In some research these polymers also possess the controlled release of drug. A variety of polymers have been discovered which includes, synthetic as HPMC, HEC, Chitosan, Carbopol and natural as gelatin, albumin, starch. Utility of synthetic polymers are associated with large numbers of risk such as high cost, toxicity, environmental pollution during synthesis, non renewable sources, side effects and poor patient compliance.[8] These limitations of synthetic polymers may be avoided by utilization of natural polymers as they are biodegradable, chemically inert, less expensive, nontoxic, and widely available.[1,8]Natural products are now accepted worldwide due to their biodegradability, which leads low chance of riskduring uses.

Nasal administration can therefore be used as an alternative to oral administration of for exampletablets and capsules if a fast effect is desired or if the drug is extensively degraded in the gut orliver. Therapy through intranasal administration has been an accepted form of treatment in theAyurvedic system of Indian medicine. Historically, nasal drug delivery system has received interest since ancient times Nasal administration can be used to deliver drugs for either local orsystemic effect. Locally acting drugs are for example decongestants and allergy treatments.Examples of systemically active drugs available as nasal sprays are migraine drugs, nicotinereplacement and hormone treatments. In order to formulate a nasal formulation with desirableperformance and commercial attributes, the drug properties, delivery system and nasalphysiology should all be considered and understood from the early stages of a product development. It is advisable to focus on maximizing the residence time and ensuring an efficientabsorption of drug. A successful nasal formulation program involves detailed consideration ofthe interactions between formulation composition, device design, delivery system and thepatient's pathological condition. If a nasal formulation is delivered to the target site of absorption(turbinates), benefits can be gained from increased absorption and/or decreased dosagerequirements. There may also be a reduction of taste of the drug because of minimum or reducedswallowing of the administered drug. Currently, tip aperture design pumps are available toadminister formulations in an upward direction. Because the turbinates are located at the sides ofthe nostrils , the entire dose volume cannot be administered to the target site of absorption. Thisalso leads to swallowing of part of the dose. It may be possible to design a side aperture pump todirect the entire dose volume directly to the absorption site, the turbinate’s, for more efficient(target) nasal delivery. Nasal sprays for local effect are quite common. Several antimigrainedrugs are also currently administered by nasal administration because a fast effect is desired andoral administration can be prohibited by nausea. Peptide drugs (hormone treatments) are alsoavailable as nasal sprays, in this case to avoid drug degradation after oral administration. Thepeptide analogue desmopressin is, for example, available for both nasal and oral administration.

The bioavailability of the commercial tablet is 0.1% while that of the nasal spray is 3-5%according to the SPC (summary of product characteristics). Other potential drug candidates fornasal administration include anaesthetics, antiemetics and sedatives that all benefit from a fastonset of effect.[5]

Nasal drug delivery is a useful delivery method for drugs that are active in low doses and show no minimal oral bioavailability. The nasal route circumvents hepatic first pass elimination associated with the oral delivery: it is easily accessible and suitable for self-medication

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Currently, to classes of nasally delivered therapeutics are on the market. The first one comprises low molecular weight and hydrophobic drugs for the treatment of the nasal mucosaand sinus, including decongestants, topical steroids, antibiotics and other (OTC) products. Thesecond class encompasses a few drugs, which have sufficient nasal absorption for displaying systemic effects Important candidates are the compounds, generally administered by injectionand hardly absorbed after oral administration, due to their instability in gastrointestinal tract,poor absorption properties, and their rapid and extensive biotransformation. Therefore, nasaldelivery is promising alternative route for the administration of peptides and protein drugs inparticular.

Nasal mucosa has been considered as a potential ad-ministration route to achieve fast and higher level of drug absorption because it is permeable to more compounds than the gastrointestinal tract due to lack of pancreatic and gastric enzymatic activity, neutral pH of the nasal mucus and less dilution by gastrointestinal contents[8]. In recent years many drugs have been shown to achieve better systemic bioavailability through nasal route than by oral administration. Nasal therapy, has been recognized form of treatment in the Ayurvedic systems of Indian medicine, it is also called "NASAYA KARMA" [9]. Intranasal drug delivery – which has been practiced for thousands of years, has been given a new lease of life. It is a useful delivery method for drugs that are active in low doses and show no minimal oral bioavailability such as proteins and peptides [10]. One of thereasons for the low degree of absorption of peptides and proteins via the nasal route is rapid movement away from the absorption site in the nasal cavity due to the mucociliary clearance mechanism [11.] The nasal route circumvents hepatic first pass elimination associated with the oral delivery. IN non-invasive, essentially painless, does not require sterile preparation, and is easily and readily administered by the patient or a physician, e.g., in an emergency setting. Furthermore, the nasal route may offer improved delivery for "non-Lipinski" drugs [12]. Drug candidates ranging from small metal ions to large macromolecular proteins have been tested in various animal models[9].

ADVANTAGES [13]

Drug degradation that is observed in the gastrointestinal tract is absent.

- Hepatic first pass metabolism is avoided.
- Rapid drug absorption and quick onset of action can be achieved.
- The bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.
- The nasal bioavailability for smaller drug molecules is good.
- Drugs that are orally not absorbed can be delivered to the systemic circulation by nasal drug delivery.
- Studies so far carried out indicate that the nasal route is an alternate to parenteral route, especially, for protein and peptide drugs.
- Convenient for the patients, especially for those on long term therapy, when compared with parenteral medication.
- Drugs possessing poor stability in g.i.t. fluids are given by nasal route.
- Polar compounds exhibiting poor oral absorption may be particularly suited for this route of delivery

LIMITATIONS [14,15]

- The histological toxicity of absorption enhancers used in nasal drug delivery system is not yet clearly established.

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- Relatively inconvenient to patients when compared to oral delivery systems since there is a possibility of nasal irritation.
- Nasal cavity provides smaller absorption surface area when compared to GIT.
- There is a risk of local side effects and irreversible damage of the cilia on the nasal mucosa, both from the substance and from constituents added to the dosage form.
- Certain surfactants used as chemical enhancers may disrupt and even dissolve membrane in high concentration.
- There could be a mechanical loss of the dosage form into the other parts of the respiratory tract like lungs because of the improper technique of administration.

MUCOADHESIVE DRUG DELIVERY SYSTEM

Mucoadhesive drug delivery system are delivery system which utilizes the property of bioadhesion of certain polymers which become adhesive on hydration and can be used for targeting a drug to a particular region of the body for extended periods of time. The term "mucoadhesion" was coined for the adhesion of the polymers with the surface of the mucosal layer [83]. Bioadhesion is a phenomenon in which two materials at least one of which is biological and are held together by means of interfacial forces. The attachment could be between an artificial material and biological substrate such as adhesion between polymer and a biological membrane in case of polymer attached to the mucin layer of mucosal tissue. The term mucoadhesion is used when the mucosal layer lines a number of regions of body
including a gastrointestinal tract, urogenital tract, the airways, the ears, nose and eye. These represent potential sites for attachment of bioadhesive system and hence the mucoadhesive drug delivery system could be designed for buccal, oral, vaginal, rectal, nasal and ocular route of administration.

The nasal route of drug administration constitutes the one of the rare and recent and preferred means of drug delivery to systemic circulation of body. However nasal administration of most of the drugs in liquid dosage forms has short-term limitations due to their inability to restrain and localize at site of administration. Microspheres constitute an important part of theseparticulate drug delivery systems by virtue of their small size and efficient carrier capacity. Microspheres are the carrier linked drug delivery system in which particle size is ranges from (1-1000 μm) range in diameter having a core of drug and entirely outer layers of polymers as coating material. However, the success of these microspheres is limited due to their short residence time at site of absorption. It would, therefore be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membrane [82]. This can be achieved by coupling bioadhesion characteristics to microspheres and developing bioadhesive microspheres. Bioadhesive microspheres have advantages like efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer and specific targeting of drugs to the absorption site.

MECHANISM OF MUCOADHESION

A complete understanding of how and why certain macromolecules attach to a mucus surface is not yet available, but a few steps involved in the process are generally accepted, at least for solid systems. Several theories have been proposed to explain the fundamental mechanism of adhesion such as[16]

1) Electronic theory
2) Absorption theory
3) Diffusion theory

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4) Wetting theory
5) Cohesive theory

A General Mechanism of Mucoadhesion Drug Delivery system is shown in Figure 1.

Electronic theory

According to this theory, electron transfers occur upon contact of adhesive polymer with a mucus glycoprotein network because of difference in their electronic structures. This results in the formation of electrical double layer at the interface e.g. Interaction between positively charged polymers chitosan and negatively charged mucosal surface which becomes adhesive on hydration and provides an intimate contact between a dosage form and absorbing tissue.

Absorption theory

According to this theory, after an initial contact between two surfaces, the material adheres because of surface force acting between the atoms in two surfaces. Two types of chemical bonds resulting from these forces can be distinguished as primary chemical bonds of covalent nature and Secondary chemical bonds having many different forces of attraction, including electrostatic forces, Vander Walls forces, hydrogen and hydrophobic bonds.

Diffusion theory

According to this theory, the polymer chains and the mucus mix to a sufficient depth to create a semi permanent adhesive bond. The exact depth to which the polymer chain penetrates the mucus depends on the diffusion coefficient and the time of contact. The diffusion coefficient in terms depends on the value of molecular weight between crosslinking and decreases significantly as the cross linking density increases.

Wetting theory

The wetting theory postulates that if the contact angle of liquids on the substrate surface is lower, then there is a greater affinity for the liquid to the substrate surface. If two substrate surfaces are brought in contact with each other in the presence of the liquid, the liquid may act as an adhesive among the substrate surface.

Cohesive theory

The cohesive theory proposes that the phenomena of bioadhesion are mainly due to intermolecular interaction amongst like molecule. Based upon the above theories, the process of bioadhesion can broadly be classified into two categories namely chemical (electron and absorption theory) and physical (wetting, diffusion and cohesive theory).

POLYMERS USED IN MUCOADHESIVE DRUG DELIVERY SYSTEM

Mucoadhesive polymers are water-soluble and water insoluble polymers, which are swellable networks, jointed by cross-linking agents. These polymers possess optimal polarity to make sure that they permit sufficient wetting by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to take place. Fallowing types of polymers are used in mucoadhesive drug delivery system:

1) Hydrophilic polymers
   E.g. Anionic polyelectrolytes - poly (acrylic acid) and carboxymethyl cellulose
   Cationic polyelectrolyte – chitosan
   Non-ionic polymers - poloxamer, hydroxypropyl methyl cellulose, methyl cellulose, Poly (vinyl alcohol) and poly (vinyl pyrrolidone)
2) Hydrogels
   E.g.poly acrylic acid
3) Thiolated polymers
   E.g. Chitosan- iminothiolane, poly (acrylic acid)–cysteine, poly (acrylic acid)–homocysteine, chitosan–thioglycolic acid, chitosan–thioethylamidine, alginate–cysteine, poly (methacrylic acid)–cysteine and sodium carboxymethylcellulose–cysteine, [80]
4) Lectin based polymers

IDEAL CHARACTERISTICS OF AN MUCOADHESIVE POLYMER

1. The polymer and its degradation products should be nontoxic and nonabsorable from the GIT.
2. It should be nonirritant to the mucous membrane.
3. It should preferably form a strong noncovalent bond with the mucin-epithelial cell surfaces.
4. It should adhere quickly to most tissue and should possess some site-specificity.
5. It should allow daily incorporation to the drug and offer no hindrance to its release.
6. The polymer must not decompose on storage or during the shelf life of the dosage form.
7. The cost of polymer should not be high so that the prepared dosage form remains competitive

METHOD OF PREPARATION

- Preparation of Microspheres by Thermal cross-linking
- Preparation of Microspheres by Glutaraldehyde crosslinking
- Preparation of microspheres by Tripolyphosphate
- Preparation of Microspheres by Emulsification and Ionotropic gelation by NaOH
- Preparation of Ethyl cellulose Microspheres
- Spray Drying
- Solvent Evaporation
- Wet Inversion Technique
- Complex Coacervation
- Hot Melt Microencapsulation

ANATOMY & PHYSIOLOGY OF NASAL CAVITY

The nasal cavity is divided into two halves by the nasal septum and extends posterior to the nasopharynx, while the most anterior part of the nasal cavity, the nasal vestibule, opens to theface through the nostril. The nasal cavity consists three main regions are nasal vestibule, olfactory region and respiratory region. The surface area in the nose can be enlarges about 150cm by the lateral walls of the nasal cavity includes a folded structure, it is a very high surface area compared to its small volume. This folded structure consists of three turbinates: the superior, the median and the inferior [17]. The main nasal airway havingthe narrow passages,

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usually it has 1-3mm wide and these narrows structures are useful to nose to carry out its main functions. The nasal cavity is covered with a mucous membrane which can be divided into two areas; non olfactory and olfactory epithelium, in this non-olfactory area includes the nasal vestibule which is covered with skin-like stratified squamous epithelium cells, where as respiratory region, which has a typical airways epithelium covered with numerous microvilli, resulting in a large surface area available for drug absorption and transport (Sarkar 1992). In this way the mucus layer is propelled in a direction from the anterior to-wards the posterior part of the nasal cavity. The goblet cells are present in the mucus membrane which covers the nasal turbinate and the atrium; it secretes the mu-cus as mucus granules which are swelling in the nasal fluid to contribute to the mucus layer. The mucus secretion is composed of about 95% water, 2 % mucin, 1% salts, 1% of other proteins such as al-bumin, immunoglobulin s, lysozyme and lactoferrin, and b 1% lipids (Kaliner et al., 1984). The mucus secretion gives immune protection against inhaled bacteria and viruses. It also performs anumber of physiological functions. [1] It covers the mucosa, andphysically and enzymatically protects it. [2] The mucus has waterholdingcapacity.[3] It exhibits surface electrical activity.[4]Itpermits efficient heat transfer.[5]It acts as adhesive and transports particulate matter towards the nasopharynx.

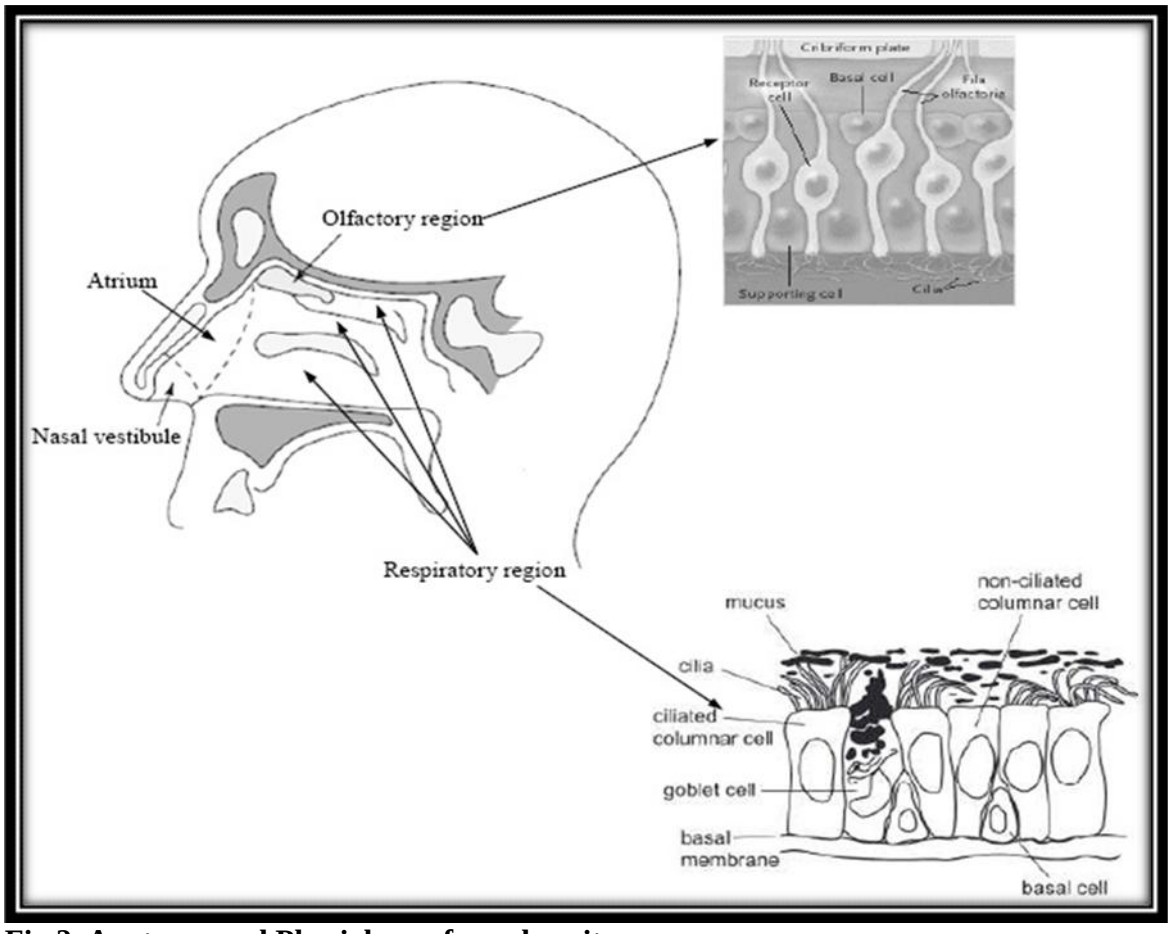

Fig.2. Anatomy and Physiology of nasal cavity

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There is mainly four parts in the nasal cavity called vestibule, atrium, respiratory region and olfactory region.Each part distinguishes from one other due to their specific characteristic, function and permeability.

Nasal vestibule

Nasal vestibule is the most anterior part of the nasal cavity, just inside the nostrils, and presents an area about 0.6 cm2 [18.] Here, there are nasal hairs, also called vibrissae, which filter the inhaled particles. Histologically, this nasal portion is covered by a stratified squamous and keratinized epithelium with sebaceous glands[18,19,20] ..These nasal vestibular characteristics are desirable to afford high resistance against toxic environmental substances but, at the same time, the absorption of substances including drugs becomes very difficult in this region[21] .

Atrium

Atrium is the intermediate area between nasal vestibule and respiratory region. Its anteriorsection is constituted by a stratified squamous epithelium and the posterior area by pseudostratified columnar cells presenting microvilli [19,20.]

Respiratory region

The nasal respiratory region, also called conchae, is the largest part of the nasal cavity and it isdivided in superior, middle and inferior turbinates which are projected from the lateral wall. These specialized structures are responsible for humidification and temperature regulation ofinhaled air. Between them there are spaces, called meatus, which are passageways where airflow is created to assure a close contact of the inhaled air with the respiratory mucosal surface. The inferior and middle meatus receive nasolacrimal ducts and paranasal sinuses which are air-filled pockets located inside the bones of the face and around the nasal cavity [22.] The nasal respiratory mucosa, considered the most important section for delivering drugs systemically, is constituted by the epithelium, basement membrane and lamina propria. The nasal respiratory epithelium consists of pseudostratified columnar epithelial cells, globet cells, basal cells and mucous and serous glands [19,20,23]. Many of the epithelial cells are covered on their apical surface with microvilli and the major part of them also has fine projections, called cilia [42]. Actually, microvilli are important to enhance the respiratory surface area, while cilia are essential to transport the mucus toward the nasopharynx. Under physiological conditions, nasal epithelium is covered with a thin mucus layer produced by secretory glands and globet cells. These ones secrete granules filled with mucin, a glycoprotein that determines the viscosity of the mucus. The nasal mucus layer is only 5 μm thick and it is organized in two distinct layers: an external, viscous and dense, and an internal, fluid and serous. Overall, nasal mucus layer consists of 95% of water, 2.5-3% of mucin, and 2% of electrolytes, proteins, lipids, enzymes, antibodies, sloughed epithelial cells and bacterial products [24,25] . Nasal mucus is indispensable or several physiological functions, such as humidification and warming of the inhaled air, and also offers physical and enzymatic protection of the nasal epithelium against several foreign compounds, including drugs. The protective action results of the adhesive characteristics of mucus to attract inhaled particles or pathogens, which are removed towards the nasopharynx by nasal MCC [26] . The presence of mucin in the nasal mucus layer is crucial because it may trap large molecular weight drugs, such as peptides and proteins[27]. The basal cells that exist in the epithelium are progenitors of other cell-types and lye on a thickened layer of collagen called basement membrane. Beneath of it, there is the lamina propria which is richly supplied with blood vessels, including many very permeable fenestrated capillaries, nerves, glands and immune cells. The last

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ones produce immunoglobulin A antibodies that confer immunological protection against bacteria and virus [28].

Olfactory region

The olfactory region is located in the roof of the nasal cavity and extends a short way down theseptum and lateral wall [41]. Its neuroepithelium is the only part of the CNS that is directlyexposed to the external environment [29]. Similarly to the respiratory epithelium, the olfactory one is also pseudostratified but contains specialized olfactory receptor cells important for smell perception [29,30]. In this area there are also small serous glands (glands of Bowman) producers of secretions acting as a solvent for odorous substances [30].

Table: 1- A feature of specific parts of nasal cavity:

Nasal parts	Characteristics	Function	Permeability	Surface area	vascularization
Vestibule	Keratinized and stratified squamous epithelialcells with nasal hairs	Support and protection	Poor	~0.6 cm^2	low
Atrium	Stratified squamous cells and pseudostratified cells	Support	Reduced	NF	low
Respiratory region	Columnar ciliated cells,columnar non ciliatedcells, globet	Support, muciliary clearance and Mucus secretion	Good	~130 cm^2	Very high
Olfactory region	Sustentacular cells, olfactory receptor 6cells,andbasal cells	Suppor and olfaction Perception	Directaccess to CNS	~15 cm^2	High

MECHANISM OF NASAL ABSORPTION

First mechanism involves paracellular route of transport, which is a passive process of absorption through nasal route. Hydrophilic drugs transport through this route. The drugs with molecular

weight greater than 1000 daltons show poor bioavailiblity[31.] Second mechanism involves transcellular process. Lipophilic drugs transport through this route. It is an active route of transport.

1. First mechanism

It involves an aqueous route of transport, which is also known as the paracellular route but slow and passive. There is an inverse log-log correlation between intranasal absorption and themolecular weight of water-soluble com-pounds. The molecular weight greater than 1000 Daltons having drugs shows poor bioavailability.

2. Second mechanism

It involves transport through a lipoidal route and it is also known as the transcellular process. It is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drug also cross cell membranes by an active transport route via carrier-mediated means or transport through the opening of tight junctions.

Intranasal Drug Delivery is mainly used for two purposes i.e. for mainly systemic delivery and for local delivery. To assess the therapeutic viability of intranasal drug delivery several approaches should be considered, attending, specifically, to the nature of pathologic condition (acute or chronic) and intended effects of drug treatment (local, systemic or at CNS). Indeed, for acutedisease conditions, the advantages afforded by intranasal drug delivery in terms of patient comfort and compliance may not be much relevant when compared with drug delivery byparenteral route. In contrast, this is particularly important to treat clinical or chronic condition.[3]

Local delivery

Intranasal administration of medicines is the natural choice for the treatment of topical nasaldisorders. Among the most common examples are antihistamines and corticosteroids forrhinosinusitis, and nasal decongestants for cold symptoms (Table 2). In these cases, intranasalroute is the primary option for drug delivery because it allows a rapid symptom relief with amore favourable adverse-event profile than oral or parenteral routes. In fact, relatively low doses are effective when administered topically [18], minimizing simultaneously the potential ofsystemic toxic effects. Recently, for instance, topical antibiotherapy has been considered inchronic rhinosinusitis in an attempt to eradicate biofilm bacteria, often resistant to systemic treatment, and still avoiding systemic toxicity.

Systemic delivery

The intranasal administration is an effective way to systemically delivery of drugs as an alternative to oral and intravascular routes. Actually, it seems to present fast and extended drug absorption [32], and it has been supported by many studies planned to compare intranasal drug delivery against oral and parenteral administration (Figure 2) [33,34,35]. Consequently, the number of drugs administered as nasal formulations intended to achieve systemic effects has widely increased. Some prominent examples include analgesics (morphine) [18,36,37], cardiovascular drugs as propranolol [37] and carvedilol [38] hormones such as levonorgestrel [39,] progesterone[38] and, hormonesinsulin [43,44,45,46]anti-inflammatory agents as indomethacin [46,47]and ketorolac [48,49], and antiviral drugs (acyclovir) [40,41,42.] Actually, there are some examples already available in the market (Table 2). These include, for instance, zolmitriptan and sumatriptan for the treatment of migraine and cluster headaches.

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Table 2:Examples of nasal formulations commercially available after prescription [18,50,51,52] Local Delivery

Drug	Brand	Main Expeints	Supplier	Main Indications
Azelastine	Astelin	Benzalkonium chloride, edetate disodium, hypromellose	Meda Pharmaceuticals	
Beclometasone	Beconase	Microcrystalline cellulose, carboxymethyl cellulose sodium, benzalkonium chloride	GlaxoSmithKline	
Budesonide	Rhinocort	Microcrystalline cellulose, carboxymethyl cellulose sodium,dextrose anhydrous	AstraZeneca	
Levocabastine	Livostin	Benzalkonium chloride, edetatedisodium, disodium phosphate	Jansen-Cilag	Management/treatment of symptoms of seasonal and perennial rhinosinusitis
Mometasone	Nasonex	Microcrystalline cellulose, carboxymethylcellulose sodium, benzalkonium chloride	Schering-Plough	
Olapatadine	Patanase	Benzalkonium chloride, dibasicsodium phosphate, edetate disodium	Alcon Laboratories	
Sodium cromoglicate	Nasalcrom	Benzalkonium chloride, edetate disodium	Sanofi-Aventis	
Triamcinolone acetonide	Nasacort	Microcrystalline cellulose, carboxymethylcellulose sodium, polysorbate 80	Sanofi-Aventis	
Mupirocin	Bactroban	Paraffin and a mixture of glycerinesters (Softisan 649)	GlaxoSmithKline	Eradication of nasal staphylococci

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Systemic Delivery

Table 3 nasal; formulations used for the purpose of systemic delivery

Estradiol	Aerodiol	Methylbetadex, sodium chloride	Servier laboratories	Hormone replacement therapy
Nicotine	Nicotrol NS	Disodium phosphate, sodium dihydrogen phosphate,citric acid	Pfizer	Smoking cessation
Cyanocobalamin	Nascobal	Sodiumcitrate, citric acid, benzalkonium chloride	Strativa pharmaceuticals	Vitamin B12 deficiency
Desmopressin	Desmospray	Sodium chloride, citric acid, benzalkonium chloride	Ferring Pharmaceuticals	Control of dehydration in diabetes insipidus
Oxytocin	Syntocinon	Citricacid, chlorobutanol, sodium chloride	Novartis	Labour induction; lactation stimulation
Salmon calcitonin	Miacalcin	Sodium chloride, benzalkonium chloride, hydrochloric acid	Novartis	Treatment of postmenopausal osteoporosis
Buserelin	Suprefact	Sodium hydroxide, sodium chloride, sodium dihydrogen phosphate	Sanofi-Aventis	Treatment of prostate cancer
Nafarelin	Synarel	Benzalkonium chloride, glacialacetic acid	Roche Laboratories	Management of endometriosis
Sumatriptan	Imigran	Potassium dihydrogen cluster headaches phosphate, dibasic sodium phosphate anhydrous	GlaxoSmithKline	Treatment of migraine and Sumatriptan Imigran Potassium dihydrogen cluster headaches
Fentanyl	Instany	Sodium dihydrogen phosphate dehydrate, disodium phosphate dehydrate	Nycomed Pharma	
Butorphanol	Stadol NS	Sodium chloride, citric acid, benzethonium chloride	Bristol-Myers Squibb	Pain management
Live attenuated influenza vaccine	FluMist	Monosodium glutamate, hydrolyzed porcine gelatin, arginine, dibasic potassium phosphate, monosodium phosphate, gentamicin sulfate	MedImmune, Inc	Flu prevention

BARRIERS TO NASAL ABSORPTION

Nasal drug delivery system is considered has a profitable route for the formulation scientist because it has easy and simple formulation strategies. Intra-nasally administered drug productstherapeutic efficacy and toxicities are influenced by number of factors . Following factors are the barriers to the absorption of drugs through nasal cavity.

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Table 4 :Barriers to nasal absorption :

Nasal Barriers	Factors to be considered
1) Physiological barriers	
a) Nasal mucus b) Nasal epithelial barrier c) Mucociliary clearance d) Pathophisiology e) Nasal metabolism f) Efflux transport system	a)Viscocity ph of mucous drug and dosage form interaction b)molecular weight, ionization constant and mode of transport c) nasal residential time and nature of dosage form d)volume of nasal secretion and permeability of nasal epithelium e) nature of the molecules (e.g. proteins and peptides) f) nature of drug molecules and duration of therapy
2) Physicochemical barriers a) Drug solubility and dissolution b) Molecular weight and size c) Compound liphophilicity d) P^H and pka	a) Nature of the dosage form , dose , pka, and polymorphism b) Less bioavailabitliy with molecular weight more than 1000 c) Affects the nose to bllod and nose to brain absorption d) Unionized ph favours for absorption

i) Low bioavailability

Lipophilic drugs are generally well absorbed from the nasal cavity compared to polar drugs. The pharmacokinetic profiles of lipophilic drugs are often identical to those obtained after anintraven-ous injection and bioavailability approaching 100%. A good examples of this is the nasal administration of Fentanyl where the *t*max for both intravenous and nasal administration have been shown to be very rapid (7 min or less) and the bioavailability for nasal anterior part of the nasal cavity can decrease clearadministration was near 80% .

Strategies to improve nasal bioavailability:

1. Nasal Enzyme Inhibitors
   e.g. bestatin, amastatin, borolucine, fusidic acids and bile salts
2. Nasal permeation enhancers
   e.g. Cyclodextrins, surfactants, saponins ,fusidic acids and phospholipids
3. Prodrug approach
   e.g.cyclic prodrugs, esters and derivatisation of C and N termini
4. Nasal mucoadhesives
   e.g. carbopol, polycarbophil, cellulose derivatives, lecithin and chitosan
5. Particulate drug delivery
   e.g. microspheres, nanoparticles and liposomes

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ii) Low membrane transport

Particles entrapped in the mucus layer are transported with it and thereby effectively cleared from the nasal cavity. The combined action of the mucus layer and cilia is called mucociliary clearance. This is an important, non-specific physiological defence mechanism of the respiratory tract to protect against noxious inhaled materials. Mucus traps the particles of dust, bacteria and drug substances and is transported towards the nasopharynx at a speed of 5 - 8 mm/min , where it is swallowed. The normal mucociliary transit time in humans has been reported to be 12 to 15 min .

Low membrane transport is the general rapid clearance of the administered formulation from the nasal cavity due to the mucociliary clearance mechanism. This is especially the case for drugs that are not easily absorbed across the nasal membrane. It has been shown that for both liquid and powder formulations, that are not mucoadhesive, the half life of clearance is in the order of 15–20 min .

Table 5: Pathologocal condition and their impact on mucociliary clearance:

Pathological condition	Mucociliary clearance
• Primary ciliary dyskinesia	Impaired: absence or dyskinetic beating cilia
• Asthma	Increased: inflammatory process and irritation Decreased: epithelial damage
• Cystic fibrosis	Impaired: dehydratation of mucus
• Viral and bacterial infections	Compromised: loss of cilia and change of mucus properties
• Diabetes mellitus	Impaired: dehydratation and microvascular damage

iii) Enzymatic Degradation

The role of the enzymatic barrier is to protect the lower respiratory airways from toxic agents;the nasal mucosa contains many enzymes such as cytochrome P450-dependent monooxygenase, carboxyl esterase and amino peptidase. Although nasal delivery avoids hepatic first-pass metabolism to some extent, the nasal mucosa provides a pseudo-first-pass effect. In addition, there are various barriers in the nasal membrane for protection from the microorganisms, allergens and irritating substances from the environment that must be overcome by drugs before they can be absorbed into the systemic circulation .Another contributing (but normally considered less important) factor to the low transport of especially peptides and proteins across the nasal membrane is the possibility of an enzymatic de-gradation of the molecule either within the lumen of the nasal cavity or during passage across the epithelial barrier. These sites both

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contain exopeptidases such as mono- and diaminopeptidases that can cleave pep-tides at their N and C termini and endopeptidases such as serine and cysteine, which can attack internal pep-tide bonds .

iv) **Protective barriers**

The first step in the absorption of drugs from the nasal cavity passed through the mucus. Uncharged substances with small molecular weight can easily pass through this layer.However, larger or charged particles may find it more difficult to cross. Mucin, the principalprotein in the mucus, has the potential to bind to solutes, hindering diffusion. Additionally,structural changes in the mucus layer are possible as a result of environmental changessuch as pH, temperature etc. The nasal membrane is a physical barrier and the mucociliary clearance is a temporal barrier to drug absorption across the nasal epithelium.[2]

Physicochemical properties of drugs

The influence of physicochemical characteristicsof drug molecules on the rate and extent ofgastrointestinal absorption is well understood.Therefore, in silico models have been developedto prioritize numerous drug candidates at the earlyphases of drug discovery. In same way, but withsome differences, the physicochemical propertiesof drugs (molecular weight, lipophilicity, pKa,stability and solubility) can influence nasalabsorption.[3]

Molecular weight, lipophilicity and pKa

Lipophilic drugs such as propranolol,progesterone and fentanyl are, in general, wellabsorbed from the nasal cavity, presenting after intravenous administration (Figure 4) and a nasal bioavailability near to 100%. Indeed, they are quickly and efficiently absorbed across the nasal membrane through transcellular mechanisms. However, it is important to state that this is true for lipophilic compounds presenting a molecular weight lower than 1 kDa. Theextension of nasal absorption of lipophilic drugsbigger than 1 kDa is significantly reduced . [7]On the other hand, the rate and degree of nasal absorption of polar drugs is low and highlydependent of the molecular weight. Several studies [6, 7, 9] demonstrated that the permeation of polar drugs with a molecular weight of less than 300 Da is not considerably influenced by their physicochemical properties. By contrast, the rate of permeation is highly sensitive to molecular size if it is higher than 300Da; an inverse relationship exists between rate of permeation and molecular weight [6, 7]. For some small polar molecules only a 10% bioavailability is suggested. The value goes down to 1% for large molecules such as proteins [53].The nasal membrane is predominantly lipophilic, hence, drug absorption is expected to diminish with a decrease in lipophilicity [54,55]. Thus, it is evident that polar drugs are not easilytransported across nasal membrane thereby enhancing MCC. However, if lipophilicity is too high, the drug does not dissolve easily in the aqueous environment of nasal cavity, hence, with accelerated MCC the contact time with nasal membrane diminishes resulting in a reduced permeation through the wall [56]. In general, the
passage across biomembranes is affected not only by lipophilicity/hydrophilicity, but also by the amount of drug existing as uncharged species. This depends on the drug pKa and the pH of the absorption site (5.0-6.5 in human nasal mucosa) [57,58,59]. According to pH partition theory, the non-ionized fraction of a drug is more permeable than that ionized. For the nasal mucosa, a range of studies evaluating the effect of lipophilicity and pH on the absorption of small drugs were performed [60.61,62,63,64]. All of them demonstrated that nasal absorption of weakelectrolytes

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depends on their ionization degree and the largest absorption occurs for the nonionized species. In this state, they present a higher apparent partition coefficient and, thus, they aremore lipophilic. However, drugs such asacetylsalicylic acid [60]and benzoic acid [61]showed some permeability across the membrane even in environments that they are expected to exist as the ionized species. Based on these observations, it was concluded that, for polar drugs, partition coefficient is the major factorinfluencing the permeability through nasalpharmacokinetic profiles similar to those obtained**.**

Stability

During the development of new drug formulationsbiological, chemical and physical drug stability in all process. As discussed before, the environment of nasal cavity has the ability to metabolize drugs by defensive enzymatic mechanisms, which may reduce the biological stability of nasally administered drugs [67,68].

To overcome this difficulty a variety of strategies may be followed, mainly through the use of prodrugs [69.70,71] and enzymatic inhibitors [76-79] as it will be discussed later. On the other hand, many drugs may be physicochemically instable due to hydrolysis, oxidation, isomerisation, photochemical decomposition or polymerization reactions [73]. The same holds true during the intranasal drug delivery [74.]

Solubility

Drug dissolution is a pre-requisite for any drug absorption, since only the molecularly disperse form of a drug at the absorption site may cross the biomembranes. Hence, before nasal absorption the drug must to be dissolved in the watery fluids of the nasal cavity. Thus, of the utmost importance is the appropriated aqueous drug solubility to allow enough contact with the nasalmucosa and posterior absorption [22.] However,

the absorption profile is influenced not only by drug solubility but also by the nature of pharmaceutical preparations, which have to guarantee the delivery of drug at therapeutically relevant doses. Due to the small size of nasal cavity, the allowable volume of drug solution is low for intranasal drug administration [37].studies must be a matter of the major importance Thereby, drugs poorly soluble in water and/orrequiring high doses may constitute a problem.This can be overtaken enhancing the drugaqueous solubility [73,71,76,77.]

Effect of drug formulation

Viscosity

As formulation viscosity increases, the contacttime between drug and nasal mucosa enhancesand, thereby, the potential of drug absorptionincreases. At the same time, high viscosity offormulations interferes with normal ciliarybeating and/or MCC and, thus, increases thepermeability of drugs. This has been observedduring nasal delivery of insulin [58,] acyclovir[74] and metoprolol [61.] However, sometimes, enhancing formulation viscosity does not enhancethe drug absorption. For example, Zaki et al.[22] performed a study to evaluate the influenceof formulation viscosity on the retention time ofmetoclopramide hydrochloride in nasal cavity andon its absorption. Interestingly, they observed thatalthough the residence time enhanced as viscosityincreased the drug absorption diminished. Thisobservation has been attributed to a decrease in the drug diffusion from the formulation. On theother hand, it has also been reported that theviscosity of the solution may provide a largertherapeutic period of nasal formulations [22.]

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pH

The extent of nasal absorption depends on thepKa of drug and pH at the absorption site,contributing for that also the pH of formulation.At this point, it should be stated that the pH offormulation must be selected attending to drugstability and if possible should be assured thegreatest quantity of non-ionized drug species.

However, the pH of formulation can induce nasalmucosa irritation and, hence, it should be similarto that found on human nasal mucosa (5.0-6.5)(26, 35, 120). Besides, the pH often prevents thebacteria growth [33.] In order to evaluate theeffect of pH solution on the integrity of nasalmucosa, Pujara et al. (128) dissolved drugs inphosphate buffer at different pH values in therange of 2-12. The study was performed in ratswhose nasal pH is 7.39 [20]and the resultsdemonstrated that when pH ranged from 3-10 minimal quantities of proteins and enzymes werereleased from cells, demonstrating no cellulardamages. On the contrary, if pH values werebelow 3 or above 10 damages were observedintracellularly and at membrane level.

Pharmaceutical form

Nasal drops are the simplest and the mostconvenient nasal pharmaceutical form, but theexact amount of drug delivered is not easilyquantified and often results in overdose [11].Moreover, rapid nasal drainage can occur whenusing this dosage form. Solution and suspensionsprays are preferred over powder sprays becausethe last one easily prompted the development ofnasal mucosa irritation[12]. Recently, geldeviceshave been developed for a more accuratedrug delivery. They reduce postnasal drip andanterior leakage, fixing the drug formulation innasal mucosa. This enhances the drug residencetime and diminishes MCC, thereby, potentiallyincreases the nasal absorption. Over the last years,specialized systems such as lipid emulsions,microspheres, liposomes and films have also beendeveloped to improve nasal drug delivery.

Pharmaceutical excipients

In nasal formulations, a wide variety ofpharmaceutical excipients can be found and theyare selected accordingly to their functions.Solubilizers, buffer components, antioxidants,preservatives, humectants, gelling/viscosifyingagents, and flavoring or taste masking agents aresome of the most usual excipients[11]. Althoughthey are responsible for several nasal irritations,antioxidants, preservatives, humectants and
flavoring or taste masking agents are not expectedto alter nasal drug absorption[11] Commonly used excipients that are frequently added to nasal preparations are can be listed asbelow:

Bioadhesive polymers: It can be defined as a compound that is capable of interacting withbiological material through interfacial forces and being retained on such material for prolongedperiods of time. If the biological material is a mucus membrane, the bioadhesive material is
termed as a mucoadhesive .[4]

Examples:

a) Carbopol(carboxy polyethylene)
b) Sodium carboxy methyl cellulose (SCMC)
c) Hydroxypropyl cellulose(HPC)
d) Hydroxypropylmethyl cellulose(HPMC)
e) Hydroxyl ethyl cellulose(HEC)
f) Methyl cellulose(MC)

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g) Sodium hyaluronate
h) Guar gum
i) Sodium alginate
j) Polycarbophil
k) Starch
l) Dextran

Gelling agent:
Increasing solution viscosity may provide a means of prolonging thetherapeutic effect of nasal preparations. A drug carrier such as hydroxypropyl cellulose waseffective for improving the absorption of low molecular weight drugs but did not produce thesame effect for high molecular weight peptides.

Penetration enhancer: [9]
Unlike the most small drug molecules, some drugs and peptides donot cross the nasal membrane efficiently. As a result the nasal bioavailability in simple solutionformulation is very low. The low nasal absorption can be attributed to poor membranepermeability due to molecular size, lack of lipophilicity or enzymatic degradation. Enzymeinhibitors can be added to nasal formulation to prevent enzymatic degradation. The nasalmucosa is almost impermeable to molecular size greater than 1000 Dalton. To overcome theseproblems of poor membrane permeability most frequent used approach is the use of absorptionenhancers.
They act by one or combination of the following mechanisms:
1. Alteration of properties of mucosa layer.
2. Opening tight junctions between epithelial cells.
3. Reversed micelle formation between membranes.
4. Increasing the membrane fluidity by,
a) Extraction or leaching of membrane components.
b) Creating disorders in the phospholipids domain in the membrane.

Various types of penetration enhancers[15]:
Surfactants, Bile salts, Chelators, Phospholipids, Cyclodextrins, Polyoxyethylene-9-laurylether (BL-9) in saline solution improves the nasal absorption of hydralazine in both in-situ andin vivo nasal absorption studies in rats. Most peptides and proteins show insufficient nasalbioavailability. Number of approaches has been described to improve their systemic bioavailability.

Strategies for improving drug availability in nasal administration:
1) To improve the nasal residence time.
2) To enhance the nasal absorption.
3) To modify drug structure to change physicochemical properties.

Buffers:
Nasal formulations are generally administered in small volumes ranging from 25 to200 µL with 100 µL being the most common dose volume. Hence, nasal secretions may alterthe pH of the administrated dose. This can affect the concentration of un-ionized drug availablefor absorption. Therefore, an adequate formulation buffer capacity may be required to maintain

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Nasal pH

• Nasal secretion of adult : 5.5-6.5
• Infants and children: 5-6.7

Solubilizers:

Aqueous solubility of drug is always a limitation for nasal drug delivery insolution. Conventional solvents or co-solvents such as glycols, small quantities of alcohol,Transcutol (diethylene glycol monoethyl ether), medium chain glycerides and Labrasol(saturated polyglycolyzed C8- C10 glyceride) can be used to enhance the solubility of drugs.

Preservatives:

Most nasal formulations are aqueous based and need preservatives to preventmicrobial growth. Parabens, benzalkonium chloride, phenyl ethyl alcohol, EDTA and benzoylalcohol are some of the commonly used preservatives in nasal formulations. Mercurycontainingpreservatives have a fast and irreversible effect on ciliary movement and should notbe used in nasal systems.

Antioxidants:

A small quantity of antioxidants may be required to prevent drug oxidation.Commonly used antioxidants are sodium metabisulfite, sodium bisulfite, butylatedhydroxytoluene and tocopherol.

Humectants:

Many allergic and chronic diseases are often connected with crusts and drying ofmucous membrane. Certain preservatives/ antioxidants among other excipients are also likelyto cause nasal irritation especially when used in higher quantities. Humectants avoid nasalirritation and are not likely to affect drug absorption. Common examples include glycerin,sorbitol and mannitol.

Surfactants:

Incorporation of surfactant into nasal dosage forms could modify thepermeability of nasal membranes, which may facilitate the nasal absorption of drug.
eg. Sodium taurcholate, sodium glycolate, polysorbate 80, sodium lauryl sulphate.

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